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BODY IRON STORES AND THE RISK OF CANCER

RICHARD G. STEVENS, PH.D., D. YVONNE JONES, PH.D., MARC S. MICOZZI, M.D., PH.D., AND PHILIP R. TAYLOR, M.D.

Abstract Because of evidence that increased body iron stores are associated with an increased risk of cancer, we examined iron status and cancer risk in the first National Health and Nutrition Examination Survey, a survey of more than 14,000 adults begun in 1971, with follow-up between 1981 and 1984.

Among 242 men in whom cancer developed, the mean total iron-binding capacity was significantly lower (61.4 vs. 62.9 μmol per liter; P = 0.01) and transferrin saturation was significantly higher (33.1 vs. 30.7 percent; P = 0.002) than among 3113 men who remained free of cancer. The risk of cancer in men in each quartile of transferrin-saturation level relative to the lowest quartile was 1.00, 1.01, 1.10, and 1.37 (P = 0.02 for trend). The serum albumin level was significantly lower in men in whom cancer developed than in those who remained cancer-free.

Among women, those in whom cancer developed did not have significantly lower total iron-binding capacity or higher transferrin saturation than those who remained cancer-free. However, a post hoc examination of 5367 women (203 with cancer) yielded a relative risk of 1.3 (95 percent confidence interval, 0.9 to 1.9) associated with a very high transferrin saturation (≥36.8 percent, a value in the highest quartile among men); in 5228 women with at least six years of follow-up (149 with cancer), the relative risk associated with transferrin saturation above this level was 1.5 (1.0 to 2.2).

These results are consistent with the hypothesis that high body iron stores increase the risk of cancer in men. The possibility that a similar association exists in women requires further study. (N Engl J Med 1988; 319:1047-52.)

THE results of three previous studies have been consistent with the hypothesis that increased body iron stores are associated with an increased risk of cancer[1,2] and with increased overall death rates.[3] Two lines of evidence provide a biologic rationale for the hypothesis. First, iron can catalyze the production of oxygen radicals,[4] and these may be proximate carcinogens.[5,6] Second, iron may be a limiting nutrient for the growth and development of cancer cells; excess iron may increase the chances that cancer cells will survive and flourish.[7,8]

The single best indicator of iron stores that is practical to measure in a population is thought to be serum ferritin.[9,10] Serum ferritin and serum transferrin levels have been used in previous studies[1]; however, neither was available for the cohort used in the first National Health and Nutrition Examination Survey (NHANES I), the study employed in this report. NHANES I used transferrin saturation and total iron-binding capacity as surrogates for iron status. Total iron-binding capacity is inversely related to serum ferritin levels.[11]

We tested the hypothesis that persons in whom cancer later developed had higher transferrin saturation and lower total iron-binding capacity than those without cancer, when these indexes were measured well before the diagnosis of cancer. We then estimated the magnitude of the effect.

METHODS

NHANES I and its epidemiologic follow-up have been described previously.[12] From 1971 to 1975, a probability sample of the noninstitutionalized population of the United States was identified. Certain subgroups thought to be at excess risk of malnutrition were deliberately oversampled. A total of 14,407 adults 25 to 74 years of age were given an extensive dietary questionnaire to answer. A medical examination and hematologic and biochemical tests were performed, and anthropometric measurements were made. Subjects were traced and reinterviewed between 1981 and 1984. The follow-up period was defined as the time between the date of the initial examination and the first of the following events: the diagnosis of cancer, death, or the follow-up interview. Those lost to follow-up were excluded from the analysis.

The determination of cancer was made at the time of the follow-up interview with study subjects or proxies and was based on hospital records or death certificates. The date of the first hospital admission was used as the date of incidence. For subjects with only a death certificate, the date of death was used as the date of cancer

From Battelle, Pacific Northwest Laboratories, Richland, Wash. (R.G.S.), and the Cancer Prevention Studies Branch, National Cancer Institute, Blair Bldg., Bethesda, Md. (D.Y.J., M.S.M., P.R.T.). Address reprint requests to Dr. Stevens at Battelle, Pacific Northwest Laboratories, Richland, WA 99352.

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incidence. Twenty-three subjects were found to have cancer at the time of the initial interview. Among the remaining 14,384, a total of 1092 subjects could not be traced. A total of 858 incident cancers were identified. There were 7858 women with 398 cancers and 5434 men with 460 cancers. Because preclinical cancer may affect serum chemistry values, analyses were restricted to 3355 men who remained alive and cancer-free for at least four years after blood was drawn and whose total iron-binding capacity was determined during the base-line examination; cancer developed in 242 of these men. Analyses in women were based on 5367 whose total iron-binding capacity had been measured and who had been followed for at least four years, 5228 of whom had been followed for at least six years; cancer developed in 203 of the 5367.

Hematologic Determinations

Blood samples were obtained by venipuncture.[13] Hemoglobin levels were determined in NHANES I mobile examination centers with use of a Coulter hemoglobinometer. Serum samples were frozen and sent to the Nutrition Biochemistry Laboratory at the Centers for Disease Control. Serum iron and total iron-binding capacity were determined spectrophotometrically with use of a modification of the automated Technicon AAII 25 method. Transferrin saturation was calculated as 100 × (serum iron/total iron-binding capacity).

Diet and Other Variables

A dietary history was sought for all subjects in the study. An interviewer questioned each subject about food consumed in the previous 24 hours, using three-dimensional food models to estimate serving sizes. Estimates of nutrient intake were based on U.S. Department of Agriculture Handbook no. 8.[14] The details of the dietary-history procedures are given by Miller.[15]

Information on cigarette smoking was collected from only about 48 percent of subjects during the base-line interview. Therefore, a more extensive smoking history was taken during the follow-up interview. These proxy interviews are believed to be reliable in the NHANES I data base.[16] The body-mass index was calculated in men (weight in kilograms divided by the square of the height in meters). Race was coded as white or other; education was coded as college or no college; alcohol ingestion — at least one drink in the preceding year — was coded as yes or no.

Statistical Analysis

The adjusted means of the variables of interest (e.g., transferrin saturation) at the time of the base-line interview were calculated in the subjects in whom cancer subsequently developed and in those remaining cancer-free. To compute these adjusted means, each factor was treated as the dependent variable in a general linear regression, with age as an independent variable and an indicator for case status.[17] In all analyses, smoking status was coded as a nominal explanatory variable with four categories: current smoker, former smoker, never a smoker, and unknown. The primary variables of interest were approximately normally distributed. The proportional-hazards model[18] was used to examine the simultaneous effects of several variables on the risk of cancer to account for survival time and to estimate magnitudes of relative risks.[19]

The crude and age-adjusted incidences of cancer were calculated for each quartile of total iron-binding capacity and of transferrin saturation. Age (10-year groups) was adjusted against the age structure of the members of the entire cohort for whom there were data on these variables and who remained alive and free of cancer for at least four years.

Relative risks for quartiles of transferrin saturation were estimated by the Mantel–Haenszel procedure adapted to cohort studies. The computer software MOX[20] was used for the calculations. The score statistic associated with the Cox model was used to determine the significance of the trend in risks as the variable of interest increased. MOX provides this score statistic for specific cancer sites as well as for other causes of death, thus allowing for the screening of many different diseases.

Results

Table 1 shows mean values for biochemical variables, adjusted for age and smoking status, at the time of the initial examination, in subjects in whom cancer subsequently developed and in those who remained cancer-free. Among 242 men in whom cancer developed, the mean total iron-binding capacity was lower (61.4 vs. 62.9 μmol per liter; $P = 0.01$) and transferrin saturation was higher (33.1 vs. 30.7 percent; $P = 0.002$) than in 3113 men who remained cancer-free. Among men who had never smoked, the mean albumin concentration in 82 in whom cancer developed was 43.6 g per liter, whereas in controls it was 44.4 g per liter ($P<0.02$). Dietary iron intake was not significantly different between cases and controls. Iron intake per kilogram of body weight was also not significantly different (data not shown). The results were similar when analyses were restricted to men 50 years of age or older at the initial examination. In men younger than 50, however, transferrin saturation in those in whom cancer developed was 30.9 percent, whereas in those in whom cancer did not develop, it was 30.0 percent ($P = 0.7$); total iron-binding capacity was 60.4 μmol per liter (337 μg per deciliter) in those in whom cancer developed and 64.1 μmol per liter (358 μg per deciliter) in those in whom it did not ($P<0.05$).

Among women, the differences in hemoglobin, total iron-binding capacity, transferrin saturation, serum iron, serum albumin, and dietary iron intake between those in whom cancer developed and those who remained cancer-free were not significantly different from 0 (Table 1).

Among men, the age-adjusted cancer incidence in each quartile of transferrin saturation was 67, 67, 69, and 93 per 10,000 person-years at risk. For total iron-binding capacity the rates were 89, 71, 79, and 64 per 10,000 person-years at risk. The age-adjusted incidence in 34 men with a total iron-binding capacity of less than 44.9 μmol per liter (251 μg per deciliter) was

Table 1. Mean Biochemical Values for Subjects in Whom Cancer Developed and Those Who Remained Cancer-free.*

Variable	Men			Women		
	Cancer	No cancer	P value	Cancer	No cancer	P value
Hemoglobin (mmol/liter)	9.6	9.6	0.65	8.6	8.6	0.26
Total iron-binding capacity (μmol/liter)	61.4	62.9	0.01	66.4	66.5	0.91
Transferrin saturation (%)	33.1	30.7	0.002	28.2	27.4	0.29
Serum iron (μmol/liter)	20.0	19.0	0.03	18.2	17.7	0.34
Serum albumin (g/liter)	43.7	44.3	0.002	43.3	43.4	0.63
Dietary iron intake (mg/day)	13.7	14.1	0.34	9.3	9.8	0.19

*Values are adjusted for age and smoking status.

138 per 10,000 person-years at risk. The rate in 304 men with transferrin saturation exceeding 44 percent was 117 per 10,000 person-years at risk.

Smoking can affect serum markers[21] and the risk of cancer. Men who were currently smokers in the NHANES I had significantly higher hemoglobin levels, significantly higher total iron-binding capacity, and significantly lower serum albumin levels than men who had never smoked. Transferrin saturation was not significantly different between smokers and nonsmokers. Women who were current smokers had significantly higher transferrin saturation and hemoglobin levels than those who had never smoked, but similar total iron-binding capacity and serum albumin levels.

Age is an important potential confounder. Among men, the Pearson correlation of age with total iron-binding capacity was −0.16; with hemoglobin, −0.17; with transferrin saturation, 0.08; and with dietary iron intake, −0.29. The correlation of dietary iron intake with total iron-binding capacity was 0.05; with hemoglobin, 0.04; and with transferrin saturation, −0.03. Among women, the correlation of age with total iron-binding capacity was −0.26; with hemoglobin, 0.09; with transferrin saturation, 0.07; and with dietary iron intake, −0.12. The correlation of iron intake with total iron-binding capacity was 0.01; with hemoglobin, 0.01; and with transferrin saturation, 0.02. A correlation of 0 indicates no linear relation of the variables, whereas a correlation of unity indicates an exact linear relation. The low correlations of dietary iron intake with the iron-status variables suggest that the dietary-intake variable was not related to iron status.

Proportional-Hazards Modeling

We fit Cox's proportional-hazards model to the men who had been followed for at least four years (Table 2). All models were controlled for smoking and contained age at initial examination as a covariable. Model 1 yielded a coefficient for total iron-binding capacity of −0.0153 ($P<0.05$); thus, the relative risk associated with a total iron-binding capacity of 35.8 μmol per liter (200 μg per deciliter) as compared with one of 71.6 μmol per liter (400 μg per deciliter) would be 1.7 (95 percent confidence interval, 1.02 to 2.94). Model 2 yielded a transferrin-saturation coefficient of 0.0125 ($P<0.02$); thus, the relative risk associated with a transferrin saturation of 40 percent as compared with one of 20 percent would be 1.3 (95 percent confidence interval, 1.06 to 1.56). Model 3, which included race (white or other), education (college or no college), drink of alcohol in the past year (yes or no), body-mass index, hemoglobin level, serum albumin level, transferrin saturation, and total iron-binding capacity, yielded a coefficient for transferrin saturation of 0.013 ($P<0.04$) and for total iron-binding capacity of −0.001 ($P = 0.9$). The coefficient for the serum albumin level was −0.088 ($P<0.0005$); thus, the relative risk associated with a serum albumin level of 42 g per liter as compared with one of 46 g per liter would be 1.4 (95 percent confidence interval, 1.17 to 1.73). Analysis was restricted to 2653 men for whom quantitative data on alcohol consumption in grams per day yielded a nonsignificant effect of alcohol and had very little effect on the magnitude of the coefficients associated with the other variables.

Table 2. Estimates of the Effect of Variables on the Risk of Cancer Obtained by Fitting the Cox Proportional-Hazards Model to the 3355 Men Who Were Followed for at Least Four Years and Had Measurement of Total Iron-Binding Capacity.*

	COEFFICIENT†	SE	P VALUE
Model 1			
Age	0.073	0.007	0.0001
Total iron-binding capacity	−0.0153	0.0076	0.047
Model 2			
Age	0.072	0.007	0.0001
Transferrin saturation	0.0125	0.005	0.017
Model 3			
Age	0.07	0.008	0.0001
Transferrin saturation	0.013	0.006	0.03
Total iron-binding capacity	−0.001	0.01	0.89
Hemoglobin	0.124	0.10	0.20
Serum albumin	−0.088	0.024	0.0004
Race	−0.06	0.19	0.76
Education	−0.22	0.20	0.29
Alcohol	0.06	0.16	0.68
Body-mass index	−0.03	0.019	0.11

*Values are adjusted for smoking status.

†Coefficients are estimates of the effect per unit of the explanatory variable on the natural log of the relative risk. For example, to calculate the risk of cancer in a person with a particular level of total iron-binding capacity relative to a person with a different level, one multiplies the difference in levels by the coefficient associated with total iron-binding capacity; the natural antilog of this product is the estimate of relative risk associated with the specified difference in levels of total iron-binding capacity.

The Cox model was fitted to women who had been followed for at least four years. A model controlled for smoking and containing age, race, education, alcohol, and body-mass index yielded a relative risk of 1.3 associated with high transferrin saturation (>36.7 percent). Among women who had been followed for at least six years, the relative risk associated with high transferrin saturation was 1.5 ($P = 0.04$). A transferrin saturation of 36.7 was chosen because it was the value that identified the highest quartile among men.

Cancer Sites

Table 3 shows the mean values for the iron-related variables after adjustment for age and smoking status for each cancer site in men. No hypotheses concerning any particular cancer site were formulated before the examination of the data, so this table should be viewed as hypothesis-generating. The numbers of patients are small. Patients with stomach cancer tended to have lower transferrin saturation and higher total iron-binding capacity than subjects without cancer. Patients with cancers of the esophagus, bladder, and colon tended to have very low total iron-binding capacity and very high transferrin saturation. Patients with lung cancer had a slight elevation in transferrin saturation and a slight reduction in total iron-binding capacity.

Table 4 shows the relative risks estimated according to the Mantel–Haenszel procedure[20] stratified by smoking and age (in two-year increments) for each quartile of transferrin saturation relative to the lowest quartile. In the highest quartile, there were two cases of multiple myeloma, one of Hodgkin's disease, and two other lymphatic neoplasms; the remaining three cases of other lymphatic neoplasms occurred in the second highest quartile. None of these cancers occurred in the first two quartiles. There was no relation between the nine cases of leukemia and transferrin saturation; two cases of leukemia occurred in each of the first, third, and fourth quartiles, and three cases occurred in the second quartile.

Table 4. Relative-Risk Estimates Derived from the Mantel–Haenszel Procedure for Each Quartile of Transferrin Saturation in Men.*

Type of Cancer	No. of Men	Transferrin-Saturation Quartile (%)				P Value†
		0–22.8	22.9–29.1	29.2–36.7	≥36.8	
All types	232	1.00	1.01 (0.67, 1.52)	1.10 (0.74, 1.64)	1.37 (0.94, 2.01)	0.02
Lung	49	1.00	1.41 (0.49, 4.07)	2.04 (0.78, 5.33)	2.34 (0.92, 5.93)	0.02
Colon	12	1.00	1.76 (0.41, 20.4)	3.11 (0.27, 35.3)	4.69 (0.45, 48.7)	0.10

*Values in parentheses are 95% confidence limits.
†P values were obtained with the two-sided test for trend.

Albumin

After examining the results in women, we decided to restrict our attention to those with a transferrin saturation exceeding 36.7 percent. We reasoned that the albumin level might be important in subjects with high iron levels and not in those with low levels. Table 5 shows that serum albumin levels were significantly lower in women in whom cancer developed and who were followed for at least four years or at least six years than in those who remained cancer-free. Among the men with transferrin saturation exceeding 36.7 percent (highest quartile), the difference in the serum albumin level between those in whom cancer developed and those who remained cancer-free was greater than that in the total sample and had a smaller P value.

Discussion

Iron is an essential nutrient. It has a central role in metabolism, and severe iron deficiency leads to immune compromise.[22] Addy[23] wrote in 1986 that iron-deficiency anemia was still a serious problem in socially advantaged populations and could lead to an impressive array of maladies. However, Brock[24] asserted that too much iron may increase the chances of infection, since invading pathogens must acquire iron to flourish.[25] Crosby[26] has also warned that excessive iron fortification of food may lead to mild hemochromatosis, an effect that was seen in Swedish men.[27]

Given the high available iron content of the Western diet and the fact that the world is changing to the Western model, it is important to determine whether there are adverse long-term health consequences of high body iron stores and high dietary intake of iron. The results of the present study are consistent with those of a previous study that found evidence of a higher cancer risk associated with higher available body iron stores in men.[1] Dietary iron intake, however, was not associated with an increased cancer risk. In addition, the estimate of iron intake based on the 24-hour dietary-recall questionnaire was not associated with iron status, as reflected in the serum biochemical measures. If elevated body iron stores increase cancer risk, then the lack of an effect of diet could be due to a number of reasons, including (1) that the estimate of dietary iron intake in NHANES I, based on a single 24-hour recall, was not a good reflection of a subject's long-term dietary intake and (2) that dietary iron intake has little effect on body iron stores, unless there is severe dietary deficiency or overload. There is insufficient evidence to judge the truth of the latter assertion. The former possibility is very real. It has been estimated that at least 12 days of dietary data are needed to characterize dietary iron intake with any degree of confidence.[28]

The confounding of total iron-binding capacity and transferrin saturation with some other factor that increases cancer risk could account for our results. Age is negatively correlated with total iron-binding capacity and positively correlated with transferrin saturation. These correlations are small, and our analyses were age-adjusted. Smoking was not related to transferrin saturation in men, and total iron-binding capacity in

Table 3. Mean Values for Biochemical Variables According to the Site of Cancer in Men.*

Site of Cancer	No. of Cancers	Hemoglobin	Total Iron-Binding Capacity	Transferrin Saturation	Serum Iron	Serum Albumin	Dietary Iron
		mmol/liter	*μmol/liter*	*%*	*μmol/liter*	*g/liter*	*mg/day*
No cancer	3113	9.6	62.9	30.7	19.0	44.3	14.1
Esophagus	6	8.8†	57.4	41.2†	23.8	44.0	10.8
Stomach	8	10.1	67.0	26.4	17.7	44.2	11.4
Colon	12	10.0	61.3	38.6†	22.6†	44.9	19.2†
Rectum	10	9.6	65.3	33.7	21.2	43.9	12.6
Pancreas	11	9.1†	62.9	30.9	18.8	42.8	14.2
Lung	50	9.7	62.0	33.9†	20.7	43.9	13.0
Prostate	52	9.4†	61.4	31.4	19.4	43.1†	12.6
Bladder	9	9.7	55.8†	42.1†	22.4	40.9†	15.3
Other urinary	10	9.6	58.8	26.0	15.6	44.0	13.6
Other	74	9.7	60.9	32.7	19.6	43.9	14.3

*Variables are adjusted for age and smoking status. †P<0.05, as compared with values in men without cancer.

Table 5. Mean Serum Albumin Concentrations in Women and Men in Whom Cancer Developed or Who Remained Cancer-free with Transferrin Saturation Exceeding 36.7 Percent Who Were Followed for at Least Four or at Least Six Years.*

Group	Follow-up	Serum Albumin		P Value
		Cancer	No Cancer	
	yr	*g/liter (no. of subjects)*		
Women	4	42.5 (38)	43.6 (819)	0.05
Women	6	42.3 (30)	43.6 (813)	0.04
Men	4	42.7 (78)	44.3 (749)	0.0001

*Values are adjusted for age and smoking status.

smokers was higher than that in those who had never smoked; a confounding effect of smoking would tend to reduce the negative association of total iron-binding capacity with cancer risk, if it exists. Our analyses were stratified according to smoking status. It is still possible, however, that some other factor related to total iron-binding capacity and transferrin saturation is also related to cancer incidence.

In a previous study of male Chinese government workers in Taiwan,[1] lower hemoglobin levels were found in men with cancer than in controls. The "anemia of chronic disorders" was suggested as a possible explanation. In the present study, patients with cancer did not have lower hemoglobin levels. As in the Taiwan study, they did have significantly lower serum albumin levels than those without cancer, even when the analysis was restricted to men who were followed for at least four years after the blood sample was drawn, and those who had never smoked. In the Taiwan study, the iron-binding capability of albumin was cited as a possible mechanism.[29] The observation that albumin appears more important in reducing cancer risk among men in the highest quartile of transferrin saturation is consistent with an important secondary role of albumin in binding iron in men with high iron stores. In addition, among women with high transferrin saturation, serum albumin levels were significantly lower in those with than in those without cancer. However, these results are open to a wide variety of interpretations. In the Taiwan study, the associations of cancer with serum ferritin and transferrin levels were restricted to men over the age of 50 at the time of initial examination. In the present study, there was a significant relation between cancer and the iron markers in men 50 or older. In men under 50, however, there was a significant effect of total iron-binding capacity but a nonsignificant effect of transferrin saturation.

Iron may influence the risk for some cancer sites and not others. Cancer of the stomach in men appeared to be unrelated to markers of iron status. Cancers of the colon, bladder, and esophagus appeared to be strongly related, and cancer of the lung also appeared to be related to iron status. The relative risks for lung and colon cancers (Table 4) increased in a dose–response manner. In the Taiwan study,[1] lung cancer was strongly related to serum ferritin and transferrin levels, whereas stomach cancer was not (unpublished data). On the basis of these data, cancers of the lung, colon, bladder, and esophagus should be examined specifically in other studies. The relation of total iron-binding capacity and transferrin saturation to the risk of lung cancer could not be explained by smoking status in the NHANES I data set.

Proportional-hazards modeling of the relation of total iron-binding capacity and transferrin saturation to cancer incidence showed a significant effect of each when considered separately, but a nonsignificant effect of total iron-binding capacity when both were included in a larger model with many other covariates. Although the estimates of relative risk were small (ranging from 1.3 to 1.7), the impact of such an effect at the population level could be large, since the outcome in this study was the incidence of all cancer.

The age-adjusted incidence of cancer in men in each quartile of total iron-binding capacity and transferrin saturation was highest in the quartile reflecting the highest iron stores. In addition, in men with extremely low total iron-binding capacity (<44.9 μmol per liter [<251 μg per deciliter]), the incidence was 138 per 10,000 person-years, and in men with very high transferrin saturation (>44 percent), the rate was 117 per 10,000 person-years.

Among women, there were no significant differences between those with cancer and those without in the iron-status variables examined in this study. However, women had significantly lower hemoglobin and transferrin saturation and significantly higher total iron-binding capacity than men. This difference probably reflects lower iron stores. Since the cancer risk in men was elevated primarily in the highest quartile of transferrin saturation, we examined women in the same quartile and did find suggestive evidence of increased cancer risk. However, this association was suggested by the data and should be interpreted with caution.

An important further question is whether diet affects cancer risk. Nutritional antioxidants have received a great deal of attention in this regard.[30] The "oxidant" iron has received very little. In particular, high iron stores may interact with other agents, such as radiation, to magnify their effects.[31]

Too little iron is clearly detrimental. However, iron elevated beyond a level necessary to avoid anemia may also have adverse consequences. Our studies have attempted to focus on the effect of variations in iron stores on the risk of cancer. These variations may be well within the "normal" range in otherwise healthy persons. If elevated iron stores increase the long-term risk of cancer, and if iron intake affects iron stores, then the policy of iron fortification of food should be reconsidered. Iron supplementation for those who are not anemic may be unwise.

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RICHARD W. HUDGENS, M.D.